VETERANS HEALTH ADMINISTRATION
OFFICE OF PATIENT CARE SERVICES
TECHNOLOGY ASSESSMENT PROGRAM

Brief Overview:

Benzocaine-associated Methemoglobinemia in Dental Patients

Prepared by
Karen Flynn, DDS, MS
Program Manager

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TECHNOLOGY ASSESSMENT PROGRAM

An Effective Resource for Evidence-based Managers

VA's Technology Assessment Program (TAP) is a national program within the Office of Patient Care Services dedicated to advancing evidence-based decision making in VA. TAP responds to the information needs of senior VA policy makers by carrying out systematic reviews of the medical literature on health care technologies to determine "what works" in health care. "Technologies" may be devices, drugs, procedures, and organizational and supportive systems used in health care. TAP reports can be used to support better resource management.

TAP has two categories of products directed toward filling urgent information needs of its VA clients. TAP assigns a category to each new request based largely on the availability of studies from results of initial searches of peer-reviewed literature databases:

- The ***Short report*** is a self-contained, rapidly-produced qualitative systematic review of between 5 and 20 pages. It provides sufficient background information and clinical context to its subject technology to be accessible to a wide audience, including non-clinician managers.

- The ***Brief overview*** originated as an internal memo to VA clients with both well-defined and urgent information needs. It usually comprises 2 to 10 pages and assumes sufficient existing knowledge regarding clinical context and technology issues by its readers to omit these components of other TAP products. It often requires some additional reading of documents (provided with the overview for the client) to obtain a full and comprehensive picture of the state of knowledge on the topic.

All TAP products are reviewed internally by TAP's physician advisor and key experts in VA. Additional comments and information on this report can be sent to:

VA Technology Assessment Program • Office of Patient Care Services
Boston VA Healthcare System (11T) • 150 S. Huntington Ave. • Boston, MA 02130
Tel. (857) 364-4469 • Fax (857) 364-6587 • VATAP@med.va.gov

A SUMMARY FOR HTA REPORTS

VATAP is a member of the International Network of Agencies for Health Technology Assessment (INAHTA) [www.inahta.org]. INAHTA developed this checklist© as a quality assurance guide to foster consistency and transparency in the health technology assessment (HTA) process. VATAP will add this checklist© to its reports produced since 2002.

This summary form is intended as an aid for those who want to record the extent to which a HTA report meets the 17 questions presented in the checklist. It is NOT intended as a scorecard to rate the standard of HTA reports – reports may be valid and useful without meeting all of the criteria that have been listed.

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Item	Yes	Partly	No
Preliminary			
1. Appropriate contact details for further information?	√		
2. Authors identified?	√		
3. Statement regarding conflict of interest?			√
4. Statement on whether report externally reviewed?		√	
5. Short summary in non-technical language?			√
Why?			
6. Reference to the question that is addressed and context of the assessment?	√		
7. Scope of the assessment specified?	√		
8. Description of the health technology?	√		
How?			
9. Details on sources of information?	√		
10. Information on selection of material for assessment?	√		
11. Information on basis for interpretation of selected data?	√		
What?			
12. Results of assessment clearly presented?	√		
13. Interpretation of the assessment results included?	√		
What Then?			
14. Findings of the assessment discussed?	√		
15. Medico-legal implications considered?			√
16. Conclusions from assessment clearly stated?	√		
17. Suggestions for further actions?	√		

BRIEF OVERVIEW: BENZOCAINE-ASSOCIATED METHEMOGLOBINEMIA IN DENTAL PATIENTS

BACKGROUND

In February, 2006, the US Food and Drug Administration (FDA) issued "*a Public Health Advisory to notify healthcare professionals and patients about adverse events, including methemoglobinemia, associated with the use of benzocaine sprays in the mouth and throat. Benzocaine sprays are used in medical practice for locally numbing mucous membranes of the mouth and throat for minor surgical procedures or when a tube must be inserted into the stomach or airways.* On February 8, 2006, the Veterans Health Administration (VA) announced the decision to stop using benzocaine sprays for these purposes.*"* (FDA MedWatch, February 16, 2006)*.* Topical benzocaine (as **gel** rather than spray) is also widely used in dentistry, so VHA's Assistant Under Secretary of Health for Dentistry requested that TAP identify published reports of methemoglobinemia associated with use of topical benzocaine gel in dental patients.

According to the VHA Pharmacy Benefit Management Strategic Healthcare Group (PBM) policy guidance (PBM, 2006) drafted in response to the FDA announcement: *"Benzocaine-acquired methemoglobinemia has been thoroughly documented in the literature, although its mechanism is not well established. Clinical methemoglobinemia, unless reversed with methylene blue, is associated with increased morbidity and mortality...the number of benzocaine-acquired methemoglobinemia case reports appearing in the literature is approximately two hundred".* While comprehensive and providing a 75-item reference list, the PBM draft covers neither the literature necessary to definitively prove an association of benzocaine with methemoglobinemia, nor that documenting the strength of any association. These omissions prompted TAP to amend its charge from the Assistant Under Secretary for Dentistry to include documentation that an association is real rather than spurious, [i.e., attributable to another variable that tends to occur with **both** the exposure (topical benzocaine) **and** the disease (methemoglobinemia) of interest]. This overview, therefore:

1. surveys literature on the existence and strength of an association between topical benzocaine and methemoglobinemia;
2. puts that survey in the context of dentistry.

METHODS

Search strategy

TAP searched MEDLINE and EMBASE© from the inception of each (1951 and 1974, respectively) to the present. Search terms were topical benzocaine, adverse reactions, complications, methemoglobinemia, dental, epidemiology, and specific study types such as case-control or cohort, the latter two for the added part of our charge. TAP retrieved full-text articles for any citations apparently relevant to a clinical dental setting (oral administration of topical benzocaine), published in dental journals, or contributing to the

evidence for an association. Finally, additional full-text citations from review of reference lists of articles initially retrieved were identified.

All retrievals were read and abstracted by a single reviewer (KF).

Analytic framework

The progression of epidemiologic studies confirming the existence and strength of an association between exposure and disease is well-documented (Ibrahim, 1985; Fletcher, 1988; Lilienfeld and Stolley, 1994): it begins with observational, hypothesis-generating studies such as single case or case series reports, progresses through analytic, hypothesis-testing studies (case-control or cohort, from which relative risk or estimates can be calculated), and culminates in the randomized controlled trial confirming causality. Until analytic or experimental studies (case-control, cohort, or randomized controlled trial) have been conducted, accumulating numbers of case reports, case series, or narrative reviews contribute little to the evidence for existence or strength of an association. While case reports are directly relevant to TAP's charge, narrative reviews are excluded from the tables below.

RESULTS

The 75 references in the VHA PBM draft (2006) include only two from dental journals (Carroll, 2005; Wilburn-Goo, 1999); the former does not document a dental case, but rather reports on a patient undergoing transesophageal echocardiography as part of a work up for transient ischemic attack and receiving benzocaine spray to the pharynx (Table 1), while the latter is a narrative review lacking primary clinical data and excluded from further discussion here. The TAP searches detailed above yielded a total of 39 citations, of which nine were retrieved and seven ultimately abstracted as directly relevant to the Assistant Under Secretary of Health for Dentistry's concerns as amended by TAP.

Table 1 abstracts the three dental or dental journal studies contributing to this overview, while Table 2 abstracts the two substantial case series and the only two published case-control studies identified by our searches.

Table 1. Reports of methemoglobinemia in dental patients, after oral topical benzocaine, or published in dental journals

Reference	Study design	Setting	Results/comments
Klein (1983)	Case report	5.5 yo male patient in oral surgery clinic for removal of arch bars with 20% topical benzocaine applied for 5 minutes. Re-presentation to clinic with toxic methemoglobinemia (15 minutes after discharge, 20 minutes after benzocaine application).	The patient was treated with methylene blue, admitted overnight, and discharged next morning.
Gilman (1997)	Letter with case repot	Emergency room: 32 yo make patient self-medicating with acetaminophen/oxycodone combination plus Ambesol (20% benzocaine) for toothache.	The patient was treated with methylene blue, monitored in ICU, and discharged the next day.
Carroll (2005)	Case report	59 yo female undergoing transesophageal echocardiography for evaluation of cardioembolic source for TIA. Prior to procedure, she received 20% benzocaine spray. 90 minutes later, methemoglobinemia was diagnosed clinically. Off-site lab results showed methemoglobin concentration = 55%.	The patient was treated with two methylene blue infusions and recovered to an adequate oxygen saturation.

Table 2. Studies documenting existence and strength of an association between topical benzocaine and methemoglobinemia

Reference	Study design	Setting	Results/comments
Ash-Bernal (2004)	Case series	2 tertiary care hospitals (Baltimore) and associated outpatient clinics over 28 months	138 cases: • 1 fatality, 3 near-fatalities attributable to methemoglobinemia; • Dapsone accounted for 42% of cases; • 20% benzocaine spray was the etiology in 5 patients with the most elevated methemoglobinemia levels; • 94% of patients were anemic; • Cases occurred in "many areas of the hospital, including outpatient clinics", but dental clinics are not specified. Conclusions: *"Drugs that cause acquired methemoblobinemia are ubiquitous in both the hospital and the outpatient setting. Acquired methemoglobinemia is a treatable condition that causes significant morbidity and even mortality. We hope that a heightened awareness of methemoglobinemia will result in improved recognition and treatment. Primary prevention efforts have the potential to reduce the morbidity and mortality associated with this condition."*
Moore (2004)	Case series	818,439 adverse event reports to FDA, November 1997-March 2002	198 reported events of all types associated with benzocaine: • 132 cases (66.7% involved definite or probable methemoglobinemia; • Methemoglobinemia cases: 107 serious adverse events (8.1%); 2 deaths (1.5%); • In 123 of the methemoglobinemia cases (93.2%), product was a spray; in 2 cases (1.5%) a lozenge; 1 case, a gel; • In 69 cases specifying a dose, 37 (53.6%) indicated a single spray of approximately the correct dose. Conclusions: *"health professionals involved in endoscopy, intubation, bronchoscopy, or similar invasive procedures using benzocaine-containing spray should know that (1) administration may cause MHb with potentially serious consequences; (2) identifying the reaction to benzocaine usually requires co-oximetry (although it can be implied by symptoms), and (3) treatment involves immediate intravenous administration of 1 to 2 m/.kg of methylene blue."*
Zeman (2002)	Nested case-control	30 cases, 50 controls controls: methemoglobinemia among children and their parents in the Transylvania region of Romania • Exposure: dietary and environmental nitrate/nitrite;	Univariate and multifactorial analyses of risk factors: • Methemoglobinemia is most strongly associated with nitrate/nitrate exposure through dietary route ($p = 0.0318$), via feeding of formula and tea made with water containing high levels of nitrate; • Breast feeding protects infants < 6 months of age ($p = 0.0244$); • Diarrheal disease has a significant role for some individuals (likelihood ratio, 4.323, $p = 0.0376$).

Reference	Study design	Setting	Results/comments
		• Ranked risk factors: presence, absence, severity of diarrheal disease; use of vitamin supplements, presence, absence, duration of breast feeding; first generation relatives with methemoglobinemia.	Conclusions: *"Univariate and multifactorial analyses of risk factors for MHG from the case-control perspective underscore that, for this population, MHG is most strongly associated with nitrate/nitrite exposure through the dietary route (p = 0.0318), via feeding of formula and tea made with water with high levels of nitrates. "*
Askew (1994)	Case-control	New Jersey elementary school children experiencing methemoglobinemia in 1992: • Cases: 29 students meeting laboratory definition of methemoglobinemia; • Controls: 52 children (every third name from a school roster).	All 29 cases and 17/52 controls (33%) ate soup during the school lunch (OR, undefined, CI lower limit, 16.1) • Two pots of soup were prepared from ready-to-serve-cans, which were diluted with water and enriched with a commercial flavor enhancer; • The school's boiler, dormant for 5 months was restarted on the morning of the outbreak and also served as a tankless water heater; • Laboratory analysis of the soup: abnormally high quantity of nitrate (459 ppm), while undiluted soup from the same lot had 22 ppm, and flavor enhancer had 2.2ppm • Nitrites were present in the hot potable water system (4-10 ppm) and absent in the cold potable water system. Conclusions: *"This outbreak of methemoglobinemia due to nitrite poisoning was traced to soup contaminated by nitrates in a boiler additive. Nitrites are ubiquitous and potentially hazardous inorganic ions. Extreme caution should be used when the possibility for toxic human exposure to nitrites exists."*

Abbreviations: MtHg, methemoglobinemia
OR, odds ratio
CI, 95% confidence interval
Ppm, parts per million
TIA, transient ischemic attack
yo, year old

CONCLUSIONS AND DISCUSSION

TAP's searches yielded a smaller number of citations than those of the searches conducted for PBM (2006). Discrepancies likely are due to TAP's focus on the dental setting and specific study types when conducting its searches, versus PBM's broader and longer set of search terms.

Although FDA is aware of adverse events apparently related to benzocaine sprays, it is not planning action to remove the drugs from the market (FDA Public Health Advisory, February 10, 2006). TAP's review of this topic indicates that methemoglobinemia is an uncommon event that can also be associated with nitrates, which are ubiquitous environmental chemicals and for which an association of methemoglobinemia with exposure has been more rigorously researched. Therefore, we conclude that an association between methemoglobinemia and topical benzocaine as used in dentistry is insufficiently proven for it to be the basis of major clinical policy or formulary change.

POLICY DECISION

The Office of the Assistant Under Secretary of Health for Dentistry recommended that topical benzocaine gel as used in dentistry be omitted from restrictions on benzocaine spray within VHA.

REFERENCES

Ash-Bernal R, Wise R, Wright SM. Acquired methemoglobinemia: a retrospective series of 138 cases at 2 teaching hospitals. *Medicine,* 2004; 83: 265-273.

Askew GL, Finelli L, Genese CA, Sorhage FE, Sosin DM, Spitalny KC. Boilerbaisse: an outbreak of methemoglobinemia in New Jersey in 1992. *Pediatrics,* 1994; 94: 381-384.

Carroll A, Sesin GP. Case study of benzocaine-induced methemoglobinemia. *Journal - Oklahoma Dental Association,* 2005; 97: 26-27.

FDA. Accessed: February 16, 2006. FDA, FDA Public Health Advisory: Benzocaine Sprays marketed under different names, including Hurricaine, Topex, and Cetacaine-1. Available: February 10, 2006. http://www.fda.gov/cder/drug/advisory/benzocaine.htm.

Fletcher RH, Fletcher SW, Wagner EH. Clinical Epidemiology: The Essentials. 2nd. Baltimore: Williams & Wilkins, 1988.

Gilman CS, Veser FH, Randall D. Methemoglobinemia from a topical oral anesthetic. *Academic Emergency Medicine,* 1997; 4: 1011-1013.

Ibrahim M. Epidemiology and Health Policy. Rockville: Aspen Systems Corporation, 1985.

Klein SL, Nustad RA, Feinberg SE, Fonseca RJ. Acute toxic methemoglobinemia caused by a topical anesthetic. *Pediatric Dentistry,* 1983; 5: 107-108.

Lilienfeld DE, Stolley PD, Lilienfeld AM. Foundations of Epidemiology. 3rd. New York: Oxford University Press, 1994.

Moore TJ, Walsh CS, Cohen MR. Reported adverse event cases of methemoglobinemia associated with benzocaine products. *Archives of Internal Medicine,* 2004; 164: 1192-1196.

Wilburn-Goo D, Lloyd LM. When patients become cyanotic: acquired methemoglobinemia. *Journal of the American Dental Association,* 1999; 130: 826-831.

Zeman CL, Kross B, Vlad M. A nested case-control study of methemoglobinemia risk factors in children of Transylvania, Romania. *Environmental Health Perspectives,* 2002; 110: 817-822.

TECHNOLOGY ASSESSMENT PROGRAM

Mission Statement

To enhance the health of veterans and the nation by providing and fostering technology assessment for evidence-based health care

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Integrity and pride in the work that we do

Quality products that are clinically valid and methodologically transparent

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